

Melatonin, insomnia and the use of melatonergic drugs

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Summary

Due to inconsistency among reports on the therapeutic efficacy of melatonin, attention has been focused on the development of more potent melatonin analogues with prolonged effects. Melatonergic drugs, ramelteon and agomelatine have been effective in treating either sleep disorders or sleep disturbances associated with depressive disorders. MT₁ and MT₂ melatonergic receptor agonist, ramelteon, was found effective in increasing total sleep time and sleep efficiency, and in reducing sleep latency in patients with insomnia. No reduction in its efficacy was found even after 6-12 months of continuous use. The mechanism of sleep promoting action of ramelteon is entirely different from that of conventional hypnotics that are in use today. Ramelteon's use is not associated with any adverse effects even after six months to one year after its continuous usage. Another melatonergic drug, agomelatine, has also been found effective in improving sleep efficiency and quality, and this action of agomelatine is suggested to be one of the major mechanism by which agomelatine ameliorates depressive symptoms in patients with major depressive disorders and bipolar disorders.

Key Words : Melatonin, ramelteon, insomnia, agomelatine, depressive disorder.

1. Introduction

Melatonin (N-acetyl-5-methoxytryptamine), first identified by Lerner et al. (1958), is the major neurohormone secreted from the pineal gland mainly during dark hours of the night and is released in higher concentrations into the cerebrospinal fluid (Tricoire et al., 2003). The circadian pattern of pineal melatonin secretion is regulated by suprachiasmatic nucleus (SCN) of the hypothalamus. A major portion of the SCN is projected to the subparaventricular zone of the hypothalamus from where fibers proceed to terminate in the areas involved in sleep-wake regulation (Saper et al., 2005b). Sleep regulation involves interaction of two separate mechanisms namely an endogenous biological-clock that drives the circadian-rhythm of sleep-wake cycle (process-C) and a homeostatic process (process-S) that influences sleep-propensity which is determined by the duration of previous sleep episodes (Borbely, 1982). These two processes interact continuously and determine the consolidated bout of sleep at night and consolidated bout of wakefulness during daytime. Melatonin has a role in sleep regulation,

since its nocturnal rise leads to "opening of the sleep gate" and augmentation of sleep propensity (Dijk and Cajochen, 1997).

Importance of melatonin in both initiation and maintenance of sleep has been demonstrated (Cajochen et al., 2003). In diurnal animals and in human beings the onset of melatonin secretion has been shown to coincide with the timing of increase in nocturnal sleep propensity (Lavie, 1997). Since melatonin has both hypnotic and chronobiotic properties, it has been used for treatment of age-related insomnia and other primary and secondary insomnia (Zhdanova et al., 2001), and prolonged release of melatonin preparations are also effective in treating insomnias (Wilson et al., 2010).

Melatonin has also been used successfully for treatment of sleep disturbances due to disruptions of the circadian time keeping system like jet-lag, shift-work disorder or delayed sleep phase syndrome (Arendt et al., 1997; Srinivasan et al., 2010b). The high density of MT₁ and MT₂ melatonin receptors in the hypothalamic SCN confirms that melatonin regulates sleep and the sleep-

wakefulness cycle by acting on both these receptors (Reppert et al., 1994; Dubocovich et al., 2010).

As melatonin has a short-half life (less than 30 min) its efficacy in promoting and maintaining sleep has not been uniform in the studies that have been undertaken so far. Hence, the need for the development of melatonin agonists with a longer duration of action on sleep regulatory structures in the brain has been felt (Turek and Gillette, 2004). Recently, melatonergic chrono-hypnotic drug, ramelteon, has been introduced for treatment of primary insomnia and has been effective in improving sleep quality and efficiency when compared to melatonin or slow release preparations (Srinivasan et al., 2012).

2. Insomnia

Insomnia is a sleep disorder characterized by poor quality of sleep with symptoms like difficulty in falling asleep, frequent awakenings during night time, early morning awakenings, etc., resulting in fatigue, decreased memory, and impaired performance with a negative impact on health and quality of life. It is most common among elderly people and is the major cause for impairment of physical and mental health (Van Someren, 2000). Nearly 30 to 40% of the adult population suffers from mild to severe insomnia. The sequels of insomnia include fatigue, reduced alertness, irritability and impaired concentration, all these symptoms having a major negative impact on the quality of life (Cricco et al., 2001; Bastien, 2011). Due to its broad psychological and physiological impacts, insomnia has social consequences like increased risk of accidents and reduced productivity. Insomnia is treated with lifestyle modifications like relaxation and cognitive therapies, behavioral techniques like sleep hygiene (Montgomery and Dennis, 2004), and pharmacologic interventions that employ sedative-hypnotics of both benzodiazepine and non benzodiazepine drugs (Wilson et al., 2010).

3. Melatonin and sleep

The role of melatonin in the control of sleep has been investigated in both diurnal and nocturnal species. Local injection of pharmacological doses of melatonin (1 to 50 μg) in the medial preoptic area of the rat hypothalamus during daytime increased total sleep time in a dose-dependent manner mainly by increasing non-rapid eye movement (NREM) sleep (Mendelson, 2002). Melatonin has been shown to induce sleep by altering the

functions of the GABA_A-benzodiazepine receptor complex (Golombek et al., 1996). In diurnal species suppression of electrical activity in the SCN is suggested as the possible mechanism by which melatonin regulates sleep. This effect is absent in MT₁ knockout mice showing thereby the importance MT₁ receptors in melatonin's acute inhibitory effects on SCN electrical activity (Liu et al., 1997). The MT₁ and MT₂ melatonin receptor subtypes are complementary in their actions and to some extent mutually substitute for each other. The suppression of neuronal activity by melatonin is one of the possible mechanisms by which this hormone contributes to the regulation of sleep.

As melatonin deficiency is suggested as a *cause rather than a marker* for insomnia in the elderly, melatonin replacement therapy has been advocated for treating insomnia at the old age. Because melatonin is a natural hypnotic it is suitable for long term use in elderly people due to its low toxicity and limited side effect profile. Melatonin replacement therapy has been beneficial in treating elderly insomniacs since it significantly improved total sleep time (TST) and sleep quality, and reduced sleep onset latency (SOL) (Dollins et al., 1994; Garfinkel et al., 1995; Zhdanova et al., 1995, 1996; Monti et al., 1999; Brzezinski et al., 2005).

Reduced endogenous melatonin production seems to be a prerequisite for effective exogenous melatonin treatment of sleep disorders in the elderly. A meta-analysis on the effects of melatonin in sleep disturbances at all age groups (including young adults with presumably normal melatonin levels) by one of the authors of this review, revealed significant and clinically meaningful effects of exogenous melatonin on sleep quality, efficiency and latency (Brzezinski et al., 2005). However, another meta-analytical study could not find melatonin as effective in increasing sleep efficacy (SE) and reducing SOL in old subjects (Buscemi et al., 2006).

The relationship between sleep disturbances and low nocturnal melatonin production was investigated in a large population of insomniacs aged 55 years or more. Elderly insomniacs with sleep problems excreted 9.0 ± 8.3 μg of the urinary melatonin metabolite 6-sulfatoxymelatonin per night, whereas age-matched healthy controls excreted 18.1 ± 12.7 μg of 6-sulfatoxymelatonin per night, and younger subjects

excreted 24.2 ± 11.9 μg of 6-sulfatoxymelatonin per night. It was also observed that half of the elderly insomniacs excreted less than 8.0 μg of 6-sulfatoxymelatonin per night. Within this subpopulation of 372 subjects, 112 had urinary 6-sulphatoxy melatonin values lower than 3.5 μg per night (Dijk and Cajochen, 1997).

Studies carried out using 0.3-1 mg doses of melatonin, that attained in circulation “physiological melatonin levels”, have shown that melatonin reduced sleep latency (SL) and increased SE when administered to healthy human subjects during evening (Dollins et al., 1994). However, in most studies higher doses of melatonin (2-6 mg) were needed to be given to obtain the desired effects. Brain imaging studies in awake subjects show that melatonin modulates brain activity pattern to one that of resembling actual sleep (Gorfine et al., 2006). Despite clinical studies, the general efficacy of melatonin as a sleep-promoting substance has been a subject of debate (Mendelson, 1997). A possible explanation for this is that administered melatonin doses are too low. The reported lack of efficiency of melatonin could be related to the extremely short-half life of the fast release melatonin preparations, and this prompted the development of active slow release formulations (Dalton et al., 2000). Circadin[®], a 2 mg-controlled release preparation of melatonin, developed by Neurim (Tel Aviv, Israel) was approved by the European Medicines Agency (EMA) as a monotherapy for short-term treatment of primary insomnia of elderly subjects in 2007. Circadin[®], a slow-release melatonin preparation, has been shown to improve the quality of sleep and morning alertness, to reduce SOL and to ameliorate quality of life in middle-aged and elderly insomniacs (Lemoine et al., 2007; Wade et al., 2011). Generally, the poor melatonin excretors responded better to melatonin replacement therapy than other insomniacs. An unknown aspect of melatonin activity in brain with regard to its hypnotic and chronobiotic activities is the extent to which it desensitizes membrane MT₁ and MT₂ receptors. Receptor desensitization is a normal process in G-protein coupled receptors and, hence, it is expected for MT₁ and MT₂ melatonin receptors also. But in a study conducted on SCN neurons, neither *in vivo* studies (intra-peritoneal or iontophoretic application of melatonin) nor *in vitro* studies on SCN neuronal cells revealed desensitization phenomenon (Ying et al., 1998). However, desensitization phenomenon with melatonin on the membrane receptor has been observed (Gerdin et al., 2004). This raised doubt over using supra-physiological doses of melatonin for treating patients with insomnia. But melatonin receptor concentration has been shown to

increase in parallel with increase of melatonin concentration (Masana et al., 2000). This finding cast doubt on the theory of receptor desensitization phenomenon after long-term use of either melatonin or its agonists.

4. Ramelteon: The melatonergic drug for insomnia

Ramelteon (Rozerem[®], Takeda Pharmaceuticals, Japan) is a melatonergic hypnotic analog that has been demonstrated in clinical trials to be effective and safe. It is a tricyclic synthetic analog of melatonin with the chemical name (*S*)-*N*-[2-(1,6,7,8-tetrahydro-2*H*-indeno[5,4-*b*]furan-8-yl)-ethyl]propionamide (Fig. 1). In 2005 ramelteon was approved by the Food and Drug Administration (FDA) for treatment of insomnia. It is a selective agonist for MT₁/MT₂ receptors without significant affinity for other receptor sites (Kato et al., 2005; Miyamoto, 2009). *In vitro* binding studies have shown that ramelteon affinity for MT₁ and MT₂ receptors is 3-16 times higher than that of melatonin. The selectivity of ramelteon for MT₁ has been found to be greater than that of MT₂ receptors. The selectivity of MT₁ receptors by ramelteon suggests that it targets sleep onset more specifically than melatonin itself (Cajochen, 2005).

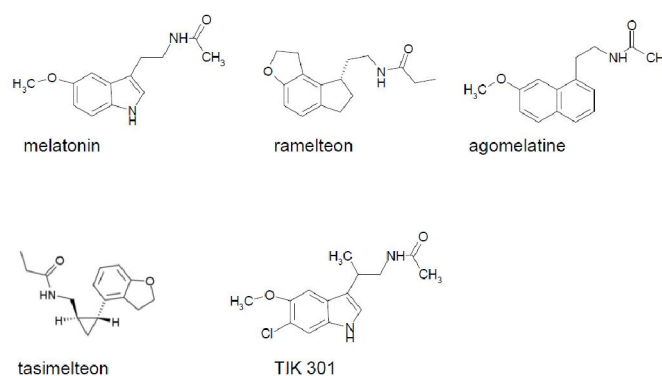


Fig. 1: Melatonin and its agonists

4.1 Pharmacokinetics of ramelteon

Ramelteon is administered usually through oral route and is absorbed rapidly by the gastrointestinal tract (84%). The half-life of circulating ramelteon is in the range of 1 to 2 hr which is much longer than that of melatonin. The influence of age and gender on the pharmacokinetics and pharmacodynamics of ramelteon were evaluated in healthy volunteers (young: 18-34 yr; elderly: 63-79 yr) after administration of a single dose of ramelteon. Compared with young individuals, the clearance of ramelteon was significantly reduced in elderly individuals. No significant effect of gender was observed (Greenblatt et al., 2007).

Ramelteon is metabolized mainly in the liver via oxidation to hydroxyl and carbonyl groups and then conjugated with glucuronide. Cytochrome P450 1A2 is the major hepatic enzyme involved in ramelteon metabolism. Four principal metabolites of ramelteon (M-I, M-II, M-III, M-IV) have been identified. Among these, M-II has been found to occur in a much higher concentrations with systemic levels 20- to 100-folds greater than ramelteon itself. Although the activity of M-II is 30-folds lower than that of ramelteon, its exposure exceeds that of ramelteon by a factor of 30. Hence, it is suggested that M-II may contribute significantly to the net clinical effect of ramelteon intake (Miyamoto, 2009).

4.2 Mechanism of ramelteon sedative-hypnotic action

Although MT_1 and MT_2 receptors are widely distributed in the brain outside the SCN (Wu et al., 2006), the high density of melatonin receptors in the SCN and their relationship to the circadian pacemaker function and, in particular, to sleep-wake cycle are highly suggestive of the SCN melatonin receptor role in sleep regulation. Ramelteon specificity for MT_1 and MT_2 melatonin receptors indicates that ramelteon's probable sleep-related site of action is in the SCN (Fig. 2) (Liu et al., 1997).

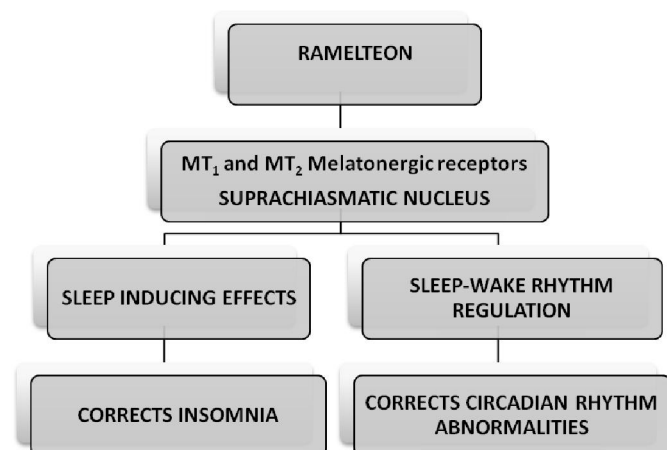


Fig. 2 Mechanism of action of ramelteon.

A “sleep-switch” model to describe the regulation of sleep-wakefulness was originally proposed by Saper et al. (2005b). It consists of “flip-flop” reciprocal inhibitions among sleep-associated activities in the ventrolateral preoptic nucleus and wakefulness-associated activities in the locus coeruleus, dorsal raphe and tuberomammillary nuclei. The SCN has an active role in promoting wakefulness as well as in promoting sleep and this depends

upon a complex neuronal network and a number of neurotransmitters released from networks of GABA, glutamate, arginine vasopressin, somatostatin, etc. (Kalsbeek et al., 2006; Raghunandanan and Raghunandanan, 2006).

Ramelteon may accelerate sleep onset by influencing the hypothalamic sleep switch downstream from the SCN in the same way as melatonin. Ramelteon promotes sleep onset through inhibition of SCN electrical activity and the consequent inhibition of circadian wake signal thereby activating the specific sleep-circuit pathway (Saper et al., 2005a).

4.3 Clinical studies on ramelteon in insomnia

The first study on the effects of ramelteon on sleep was conducted by Roth and co-workers in 2005. In this study involving 117 patients (16 to 64 yr), drawn from 13 centers in Europe, the efficacy, safety and dose response of ramelteon were examined. Each patient was randomized to a dose sequence of 4, 8, 16 or 32 mg of ramelteon. All doses of ramelteon produced a statistically significant reduction in latency to persistent sleep (LPS) and increased TST as shown by polysomnography (PSG) (Roth et al., 2005).

In a follow-up study, the same group of investigators administered ramelteon to 829 patients (>65 years) for a period of five weeks. In this double blind study ramelteon, at a dose of 4-8 mg/day, brought about a significant reduction in SOL (16% to 35%). TST was increased by both doses of ramelteon (Roth et al., 2006). In another randomized, multicenter double-blind, placebo-controlled crossover study in 107 patients and associating PSG, ramelteon was administered in doses of 4-32 mg/day. The treatment decreased LPS and increased TST significantly (Erman et al., 2006).

A short term evaluation of the efficacy of ramelteon was performed in 100 elderly subjects by administering 4 and 8 mg doses in a two night/three day period crossover design. LPS decreased, and TST and SE augmented as compared to placebo (Roth et al, 2007). Likewise, the efficacy of ramelteon in reducing SOL and in increasing TST and SE was evaluated in 371 patients administered with 8 or 16 mg of ramelteon for 5 weeks in a double-blind placebo controlled study. The results confirmed the effect of ramelteon to reduce SOL and increase SE and TST (Zammit et al., 2007).

Ramelteon hypnotic action (at an 8 mg dose) was so rapid that it caused significant reductions in SOL within a week (63% for ramelteon vs. 39.7% for placebo,

$p < 0.001$). This reduction in LPS was sustained throughout the 5 weeks of study (63 and 65.9% ramelteon vs. 41.2 and 48.9% placebo at the end of the 3rd and 5th week, respectively) (Mini et al., 2008). Reduction in LPS after ramelteon treatment was found in healthy human subjects in a 6-week long study using an 8 mg dose; in this study on healthy human subjects ramelteon increased TST also (Dobkin et al, 2009). In another 6 months study performed in 451 adults suffering from chronic insomnia, drawn from different centers across the globe (mainly USA, Europe, Russia and Australia), ramelteon consistently reduced LPS when compared to placebo (Mayer et al., 2009). The baseline LPS decreased from 70.7 to 32.0 minutes at week one and this reduction in LPS was maintained at months 1, 3, 5 and 6. No adverse effects, like next morning residual effects, rebound insomnia or withdrawal effects, were noticed (Mayer et al., 2009).

In a double-blind placebo controlled study involving large number of Japanese patients with chronic insomnia (n=1130) the efficacy and safety of 4 and

8 mg ramelteon doses were evaluated. No statistically significant differences were found in subjective SOL of patient treated with 4 mg ramelteon compared to the placebo group, while a significant increase in TST and a decrease in SOL were observed with 8 mg ramelteon (Uchimura et al., 2011).

The same investigators evaluated the efficacy and safety of ramelteon in 190 Japanese adults with chronic insomnia treated for a period of 24 weeks. TST significantly increased with ramelteon 8 mg/day dose and this was maintained for 20 weeks. In this study ramelteon was well tolerated and it did not cause residual effects, rebound insomnia, withdrawal symptoms or dependence even after 24 weeks of continuous treatment (Uchiyama et al., 2011). In all clinical studies undertaken so far to evaluate the efficacy and safety of ramelteon in various doses ranging from 4 to 32 mg/day in patients with chronic insomnia, the drug reduced SOL and increased sleep duration (Table 1). Besides acting as a sedative-hypnotic drug, ramelteon also exhibited chronobiotic properties.

Table 1. Ramelteon's beneficial effects in sleep disorders: primary insomnia

Dose (mg/day)	Duration of administration	Number of insomnia patients	Sleep onset latency (SOL) / latency to persistent sleep (LPS)	Sleep efficacy and quality	Total sleep time	Reference
4, 8, 16 and 32	2 days	107 (mean age: 37.7 yrs)	Reduction in LPS ($P < 0.001$)	Increased	Increased ($P < 0.05$)	Erman et al., 2006
4 and 8	5 weeks	829 (mean age: 72.4 yrs)	Reduced SOL	Enhanced	Increased at the end of first week, third week and fifth week	Roth et al., 2006
4	5 weeks	100 elderly patients	Reduced LPS ($P < 0.001$)	Increased	Increased	Roth et al., 2007
8 and 16	5 weeks	371 patients with chronic insomnia	Reduced SOL	Increased	Increased at all doses	Zammit et al., 2007
8 and 16	5 weeks	289 patients with chronic insomnia (mean age: 65 yrs)	Reduced LPS ($P = 0.004$)	Increased	Increased ($P = 0.009$)	Zammit et al., 2009
8	5 weeks	270 patients with chronic insomnia	63% reduction in LPS week 1 & 3, 65.9% reduction at week 5 ($P < 0.005$)	-	-	Mini et al., 2008
8	6 months	451 adults with chronic insomnia	Reduced LPS consistently	-	-	Mayer et al., 2009
	6 weeks	20 healthy peri- and post-menopausal women	Reduced LPS	Increased	Increased	Dobkin et al., 2009
4, 8 and 16	24 weeks	190 adults with chronic insomnia		Increased	Increased up to 20 weeks and then it was maintained	Uchiyama et al., 2011
4 and 8	2 weeks	1130 adults	Reduced SOL with 8 mg only	Increased in the first week	Increased	Uchimura et al., 2011
4 and 8	2 nights	65 patients with insomnia	Reduced LPS	Increased sleep quality	Increased	Kohsaka et al., 2011

In a study conducted on 75 healthy human subjects, the administration of ramelteon at doses of 1, 2, 4 and 8 mg for 6 days caused significant advancement of dim light melatonin offset (Richardson et al., 2008). Melatonergic hypnotic and chronobiotic drug ramelteon has a unique place in development of novel drugs for treatment of insomnia (Srinivasan et al., 2009).

Interestingly, a recent randomized, placebo-controlled study suggested that ramelteon can be also beneficial for treatment of ambulatory bipolar I disorder patients suffering from manic symptoms and sleep disturbances. Twenty-one outpatients with bipolar I disorder with mild-to-moderate manic symptoms and sleep disturbance were randomized to receive either ramelteon (N=10) or placebo (N=11) in an 8-week, double-blind, fixed-dose (8 mg/day) study. Ramelteon and placebo had similar rates of reduction in ratings of symptoms of insomnia, mania, and global severity of illness. However, ramelteon was associated with improvement in a global rating of depressive symptoms. It was also well tolerated and associated with no serious adverse events (McElroy et al., 2011).

5. Agomelatine, depressive disorders and insomnia

Depressive disorders are associated with sleep disturbances. In these disorders insomnia is not a consequence or an accompanying phenomenon but rather represents a major triggering factor for the development of depressive symptoms. Sleep disturbances occur in the preceding as well as during the illness period of major depressive disorders or bipolar disorders. Depressed patients experience difficulty in falling asleep, staying asleep and manifest early morning awakening (Kupfer, 2006). Agomelatine, a melatonergic drug developed by Servier Laboratories (France), is a naphthalenic compound chemically designated as [N-[2-(7-methoxynaphth-1-yl) acetamide]. It has high affinity for MT₁/MT₂ melatonergic receptors (Yous et al., 1992) and also acts as a 5-HT_{2c} receptor antagonist (Millan et al., 2003). In the study on the use of agomelatine (25 mg/day) on 165 patients and by using Leeds Sleep Evaluation Questionnaire (LSEQ) it was found that agomelatine caused earlier and greater improvements on the criteria of “getting into sleep”, and quality of sleep (Guilleminault, 2005). By using

polysomnography studies it was noted that use of agomelatine increased sleep efficiency from day 7 onwards and reached significant effect on the 42nd day, the last day of evaluation (P=0.05) (Quera-Salva et al., 2005, 2007). The action of agomelatine in improving both efficiency and quality of sleep is considered as one of the major mechanisms by which agomelatine ameliorates depressive symptoms of patients with major depressive disorder (Srinivasan et al., 2010a).

6. Conclusion

Melatonin exhibits both hypnotic and chronobiotic properties and thus has been used for inducing sleep and for treating sleep disorders of children, adults and elderly people. The results of endogenous melatonin's action in insomnia have not been consistent due to its short-half life and rapid metabolism.

Ramelteon (Rozerem®) and agomelatine, the melatonergic drugs with rapid onset and sustained actions, have been effective in treating sleep disorders and or sleep disturbances associated with depressive disorders. The melatonergic agonist ramelteon has shown promising results in the treatment and management of insomnia as revealed in the number of clinical trials that were undertaken in Europe, USA and Japan. This melatonergic drug, by acting through MT₁ and MT₂ melatonergic receptors in brain, particularly the SCN, has demonstrated superior efficacy in promoting sleep with rapid onset of action. Moreover, it did not exhibit any adverse side effects associated with the use of benzodiazepine and non-benzodiazepine sedative drugs that are in use today.

Ramelteon exerts a promising effect on sleep by amplifying day/night differences in alertness and sleep quality and by displaying effective sleep inducing effect. Because they act in a natural way in promoting sleep, their long-term use is not associated with any side effects like dependency, next-day hangover, memory impairment, cognitive dysfunction or psychomotor retardation. Agomelatine, the melatonergic antidepressant, is effective in treating patients with major depressive disorders and other mood disorders and it is attributed partly to its property of improving sleep quality and efficiency. Melatonergic drugs have a place in treatment of sleep disorders, and large clinical trials are needed to prove their efficacy and long term safety.

References

- Arendt J, Skene DJ, Middleton B, Lockley SW, Deacon S (1997) Efficacy of melatonin treatment in jet lag, shift work, and blindness. *J Biol Rhythms* **12**:604-617.
- Bastien CH (2011) Insomnia: Neurophysiological and neuropsychological approaches. *Neuropsychol Rev*. **21**:22-40.
- Borbely AA (1982) A two process model of sleep regulation. *Hum Neurobiol*. **1**:195-204.
- Brzezinski A, Vangel MG, Wurtman RJ, Norrie G, Zhdanova I, Ben-Shushan A, Ford I (2005) Effects of exogenous melatonin on sleep: a meta-analysis. *Sleep Med Rev*. **9**:41-50.
- Buscemi N, Vandermeer B, Hooton N, Pandya R, Tjosvold L, Hartling L, Vohra S, Klassen TP, Baker G (2006) Efficacy and safety of exogenous melatonin for secondary sleep disorders and sleep disorders accompanying sleep restriction: meta-analysis. *BMJ* **332**:385-393.
- Cajochen C (2005) TAK-375 Takeda. *Curr Opin Investig Drugs* **6**:114-121.
- Cajochen C, Jewett, ME, Dijk DJ (2003) Human circadian melatonin rhythm phase delay during a fixed sleep-wake schedule interspersed with nights of sleep deprivation. *J Pineal Res*. **35**:149-157.
- Cricco, M, Simonsick EM, Foley DJ (2001) The impact of insomnia on cognitive functioning in older adults. *J Am Geriatr Soc*. **49**:1185-1189.
- Dalton EJ, Rotondi D, Levitan RD, Kennedy SH, Brown GM (2000) Use of slow-release melatonin in treatment-resistant depression. *J Psychiatry Neurosci*. **25**:48-52.
- Dijk DJ, Cajochen C (1997) Melatonin and the circadian regulation of sleep initiation, consolidation, structure and sleep EEG. *J Biol Rhythm* **12**:627-635.
- Dobkin RD, Menza M, Bienfait KL, Allen LA, Marin H, Gara MA (2009) Ramelteon for the treatment of insomnia in menopausal women. *Menopause Int*. **15**:13-18.
- Dollins AB, Zhdanova IV, Wurtman RJ, Lynch HJ, Deng MH (1994) Effect of inducing nocturnal serum melatonin concentrations in daytime on sleep, mood, body temperature, and performance. *Proc Natl Acad Sci USA* **91**:1824-1828.
- Dubocovich ML, Delagrange P, Krause DN, Sugden D, Cardinali DP, Olcese J (2010) International Union of Basic and Clinical Pharmacology. LXXV. Nomenclature, classification, and pharmacology of G protein-coupled melatonin receptors. *Pharmacol Rev*. **62**:343-380.
- Erman M, Seiden D, Zammit G, Sainati S, Zhang J (2006) An efficacy, safety, and dose-response study of Ramelteon in patients with chronic primary insomnia. *Sleep Medicine* **7**:17-24.
- Garfinkel D, Laudon M, Nof D, Zisapel N (1995) Improvement of sleep quality in elderly people by controlled-release melatonin. *Lancet* **346**:541-544.
- Gerdin MJ, Masana MI, Rivera-Bermudez MA, Hudson RL, Earnest DJ, Gillette MU, Dubocovich ML (2004) Melatonin desensitizes endogenous MT₂ melatonin receptors in the rat suprachiasmatic nucleus: relevance for defining the periods of sensitivity of the mammalian circadian clock to melatonin. *FASEB J*. **18**:1646-1656.
- Golombek DA, Pevet P, Cardinali DP (1996) Melatonin effect on behavior: Possible mediation by the central GABAergic system. *Neurosci Biobehav Rev*. **20**: 403-412.
- Gorfine T, Assaf Y, Goshen-Gottstein, Y, Yeshurun Y, Zisapel N (2006) Sleep-anticipating effects of melatonin in the human brain. *Neuroimage* **31**:410-418.
- Greenblatt DJ, Harmatz JS, Karim A (2007) Age and gender effects on the pharmacokinetics and pharmacodynamics of ramelteon, a hypnotic agent acting via melatonin receptors MT₁ and MT₂. *J Clin Pharmacol*. **47**:485-496.

- Guilleminault C (2005) Efficacy of agomelatine versus venlafaxine on subjective sleep of patients with major depressive disorder. *Eur Neuropsychopharmacol.* **15 (Suppl 3)**:S419, Abstract P.2.064.
- Kalsbeek A, Perreau-Lenz S, Buijs RM (2006) A network of (autonomic) clock outputs. *Chronobiol Int.* **23**:521-535.
- Kato K, Hirai K, Nishiyama K, Uchikawa O, Fukatsu K, Ohkawa S, Kawamata Y, Hinuma S, Miyamoto M (2005) Neurochemical properties of ramelteon (TAK-375), a selective MT1/MT2 receptor agonist. *Neuropharmacology* **48**:301-310.
- Kohsaka M, Kanemura T, Taniguchi M, Kuwahara H, Mikami A, Kamikawa K, Uno H, Ogawa A, Murasaki M, Sugita Y (2011) Efficacy and tolerability of ramelteon in a double-blind, placebo-controlled, crossover study in Japanese patients with chronic primary insomnia. *Expert Rev Neurother.* **11**:1389-1397.
- Kupfer DJ (2006) Depression and associated sleep disturbances; patient benefits with agomelatine. *Eur Neuropsychopharmacol.* **16 (Suppl 5)**:S639-S643.
- Lavie P (1997) Melatonin: role in gating nocturnal rise in sleep propensity. *J Biol Rhythms* **12**:657-665.
- Lemoine P, Guilleminault C, Alvarez E (2007) Improvement in subjective sleep in major depressive disorder with a novel antidepressant, agomelatine: randomized, double-blind comparison with venlafaxine. *J Clin Psychiat.* **68**:1723-1732.
- Lerner AB, Case JD, Takahashi Y, Lee TH, Mori N (1958) Isolation of melatonin, the pineal factor that lightens melanocytes. *J Am Chem Soc.* **80**:2587.
- Liu C, Weaver DR, Jin X, Shearman LP, Pieschl RL, Gribkoff VK, Reppert SM (1997) Molecular dissection of two distinct actions of melatonin on the suprachiasmatic circadian clock. *Neuron* **19**:91-102.
- Masana MI, Benlucif S, Dubocovich L (2000) Circadian rhythm of MT1 melatonin receptor in the suprachiasmatic nucleus of the C3H/HeN mouse. *J Pineal Res.* **28**:185-192.
- Mayer G, Wang-Weigand S, Roth-Schechter B, Lehmann R, Staner C, Partinen M (2009) Efficacy and safety of 6-month nightly ramelteon administration in adults with chronic primary insomnia. *Sleep* **32**:351-360.
- McElroy SL, Winstanley EL, Martens B, Patel NC, Mori N, Moeller D, McCoy J, Keck PE Jr (2011) A randomized, placebo-controlled study of adjunctive ramelteon in ambulatory bipolar I disorder with manic symptoms and sleep disturbance. *Int Clin Psychopharmacol.* **26**:48-53.
- Mendelson WB (1997) A critical evaluation of the hypnotic efficacy of melatonin. *Sleep* **20**:916-919.
- Mendelson WB (2002) Melatonin microinjection into the medial preoptic area increases sleep in the rat. *Life Sci.* **71**:2067-2070.
- Millan MJ, Gobert A, Lejeune F, Dekeyne A, Newman-Tancredi A, Pasteau V, Rivet JM, Cussac D (2003) The novel melatonin agonist agomelatine (S20098) is an antagonist at 5-hydroxytryptamine_{2c} receptors, blockade of which enhances the activity of frontocortical dopaminergic and adrenergic pathways. *J Pharmacol Exp Ther.* **306**:954-964.
- Mini L, Wang-Weigand S, Zhang J (2008) Ramelteon 8 mg/d versus placebo in patients with chronic insomnia: post hoc analysis of a 5-week trial using 50% or greater reduction in latency to persistent sleep as a measure of treatment effect. *Clin Ther.* **30**:1316-1323.
- Miyamoto M (2009) Pharmacology of ramelteon, a selective MT1/MT2 receptor agonist: a novel therapeutic drug for sleep disorders. *CNS Neurosci Ther.* **15**:32-51.
- Montgomery P, Dennis J (2004) A systematic review of non-pharmacological therapies for sleep problems in later life. *Sleep Med Rev.* **8**:47-62.
- Monti JM, Alvarino F, Cardinali D Savio I, Pintos A (1999) Polysomnographic study of the effect of melatonin on sleep in elderly patients with chronic primary insomnia. *Arch Gerontol Geriatr.* **28**:85-98.

- Quera-Salva MA, Vanier B, Chapotot F, Moulin C, Lofaso F, Guilleminault C (2005). Effect of agomelatine on the sleep EEG in patients with major depressive disorder. *Eur Neuropsychopharmacol.* **15 (Suppl 3)**:S435.
- Quera-Salva MA, Vanier B, Laredo J, Hartley S, Chapotot F, Moulin C, Lofaso F, Guilleminault C (2007) Major depressive disorder, sleep, EEG and agomelatine: an open label study. *Int J Neuropsychopharmacol.* **10**:691-696.
- Reghunandanan V, Reghunandanan R (2006) Neurotransmitters of the suprachiasmatic nuclei. *J Circadian Rhythms* **4**:2.
- Reppert SM, Weaver DR, Ebisawa T (1994) Cloning and characterization of a mammalian melatonin receptor that mediates reproductive and circadian responses. *Neuron* **13**:1177-1185.
- Richardson GS, Zee PC, Wang-Weigand S, Rodriguez L, Peng X (2008) Circadian phase-shifting effects of repeated ramelteon administration in healthy adults. *J Clin Sleep Med.* **4**:456-461.
- Roth T, Stubbs C, Walsh JK (2005) Ramelteon (TAK-375), a selective MT1/MT2-receptor agonist, reduces latency to persistent sleep in a model of transient insomnia related to a novel sleep environment. *Sleep* **28**:303-307.
- Roth T, Seiden D, Sainati S, Wang-Weigand S, Zhang J, Zee P (2006) Effects of ramelteon on patient-reported sleep latency in older adults with chronic insomnia. *Sleep Med.* **7**:312-318.
- Roth T, Seiden D, Wang-Weigand S, Zhang J (2007) A 2-night, 3-period, crossover study of ramelteon's efficacy and safety in older adults with chronic insomnia. *Curr Med Res Opin.* **23**:1005-1014.
- Saper CB, Lu J, Chou TC, Gooley J (2005a) The hypothalamic integrator for circadian rhythms. *Trends Neurosci.* **28**:152-157.
- Saper CB, Scammell TE, Lu J (2005b) Hypothalamic regulation of sleep and circadian rhythms. *Nature* **437**:1257-1263.
- Srinivasan V, Pandi-Perumal SR, Trahkt I, Spence DW, Poeggeler B, Hardeland R, Cardinali DP (2009) Melatonin and melatonergic drugs on sleep: possible mechanisms of action. *Int J Neurosci.* **119**:821-846.
- Srinivasan V, Brezezinski A, Spence DW, Pandi-Perumal SR, Hardeland R, Brown GM, Cardinali DP (2010a) Sleep, mood disorders, and antidepressants: the melatonergic antidepressant agomelatine offers a new strategy for treatment. *Psychiatrica Fennica* **41**:168-186.
- Srinivasan V, Singh J, Pandi-Perumal SR, Brown GM, Spence DW, Cardinali DP (2010b) Jet lag, circadian rhythm sleep disturbances, and depression: the role of melatonin and its analogs. *Adv Ther.* **27**:796-813.
- Srinivasan V, Zakaria R, Othman Z, Brzezinski A, Prasad A, Brown GM (2012). Melatonergic drugs for therapeutic use in insomnia and sleep disturbances of mood disorders. *CNS Neurol Disord Drug Targets* **11**:180-189.
- Tricoire H, Moller H, Chemineau P, Malpoux B (2003) Origin of cerebrospinal fluid melatonin and possible function in the integration of photoperiod. *Reprod Suppl.* **61**:311-321.
- Turek FW, Gillette MU (2004) Melatonin, sleep, and circadian rhythms: rationale for development of specific melatonin agonists. *Sleep Med.* **5**:523-532.
- Uchimura N, Ogawa A, Hamamura M, Hashimoto T, Nagata H, Uchiyama M (2011) Efficacy and safety of ramelteon in Japanese adults with chronic insomnia: a randomized, double-blind, placebo-controlled study. *Expert Rev Neurother.* **11**:215-224.
- Uchiyama M, Hamamura M, Kuwano T, Nagata H, Hashimoto T, Ogawa A, Uchimura N (2011) Long-term safety and efficacy of ramelteon in Japanese patients with chronic insomnia. *Sleep Med.* **12**:127-133.
- Van Someren J (2000) Circadian and sleep disturbances in the elderly. *Exp Gerontol.* **35**:1229-1237.
- Wade AG, Crawford G, Ford I, McConnachie A, Nir T, Laudon M, Zisapel N (2011) Prolonged release melatonin in the treatment of primary insomnia: evaluation of the age cut-off for short- and long-term response. *Curr Med Res Opin.* **27**:87-98.

- Wilson SJ, Nutt DJ, Alford C, Argyropoulos SV, Baldwin DS, Bateson AN, Britton TC, Crowe C, Dijk DJ, Espie CA, Gringras P, Hajak G, Idzikowski C, Krystal AD, Nash JR, Selsick H, Sharples AL, Wade AG (2010) British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders. *J Psychopharmacol.* **24**:1577-1601.
- Wu YH, Zhou JN, Balesar R, Unmehopa U, Bao A, Jockers R, Van Heerikhuize J, Swaab DF (2006) Distribution of MT1 melatonin receptor immunoreactivity in the human hypothalamus and pituitary gland: colocalization of MT1 with vasopressin, oxytocin, and corticotropin-releasing hormone. *J Comp Neurol.* **499**:897-910.
- Ying SW, Rusak B, Mocaer B (1998) Chronic exposure to melatonin receptor agonists does not alter their effects on suprachiasmatic nucleus neurons. *Eur J Pharmacol.* **342**: 29-37.
- Yous S, Andrieux J, Howell HE, Morgan PJ, Renard P, Pfeiffer B, Lesieur D, Guardiola-lemaitre B (1992) Novel naphthalenic ligands with high affinity for the melatonin receptor. *J Med Chem.* **35**:1484-1486.
- Zammit G, Erman M, Wang-Weigand S, Sainati S, Zhang J, Roth T (2007) Evaluation of the efficacy and safety of ramelteon in subjects with chronic insomnia. *J Clin Sleep Med.* **3**:495-504.
- Zammit G, Schwartz H, Roth T, Wang-Weigand S, Sainati S, Zhang J (2009) The effects of ramelteon in a first night model of transient insomnia. *Sleep Med.* **10**:55-59.
- Zhdanova IV, Wurtman RJ, Lynch HJ, Ives JR, Dollins AB, Morabito C, Matheson JK, Schomer DL (1995) Sleep-inducing effects of low doses of melatonin ingested in the evening. *Clin Pharmacol Ther.* **57**:552-558.
- Zhdanova IV, Wurtman RJ, Morabito C, Piotrovska VR, Lynch HJ (1996) Effects of low oral doses of melatonin, given 2-4 hours before habitual bedtime, on sleep in normal young humans. *Sleep* **19**:423-431.
- Zhdanova IV, Wurtman RJ, Regan MM, Taylor JA, Shi JP, Leclair OU (2001) Melatonin treatment for age-related insomnia. *J Clin Endocrinol Metab.* **86**:4727-4730.